Improving Diagnostic, Prognostic & Therapeutic **Biomarkers** in Heart Disease

Professor Mark Richards

Medicine, University of Otago, Christchurch

[Link to Otago website] otago.ac.nz/cvd
BNP / NT-ProBNP

Pro-BNP

H₂N₁

76

77

108

COOH

Cardiomyocyte

Peripheral Circulation

NT-pro-BNP

H₂N₁

COOH

76

77

H₂N

108

COOH

Lam et al, JACC 2007; 49:1193
NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients

The International Collaborative of NT-proBNP Study

James L. Januzzi\(^1\), Roland van Kimmenade\(^2\), John Lainchbury\(^3\), Antoni Bayes-Genis\(^4\), Jordi Ordonez-Llanos\(^5\), Miguel Santalo-Bel\(^6\), Vidal Pinto\(^6\), and Mark Richards\(^3\)

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Diagnosis and NT-proBNP results

![Diagram showing NT-proBNP results for different CHF statuses with P<0.001 significance.]

- **Number**: 481 no prior CHF, 55 prior CHF, 720 acute CHF
- **NT-proBNP (pg/ml)**: 150, 949, 5669
- **NT-proBNP (pmol/L)**: 18, 111, 665

**Not acute CHF**
An almost perfect test in young patients..
Patient presents with acute dyspnea

History, physical exam, CXR, ECG
Measure NT-proBNP

- NT-proBNP <300 ng/L: HF very unlikely. Evaluation for a non-cardiac cause of dyspnea is recommended.
- NT-proBNP grey zone: HF possible. Clinical correlation necessary. Triage and treat as appropriate, possible early diuretics.
- NT-proBNP >age-adjusted positive: HF likely. Triage and treat as appropriate. If prior HF, evaluate for Δ >25% from “dry” NT-proBNP.
- NT-proBNP >10000 ng/L: Severe HF very likely and associated with high risk. Admit, close monitoring.


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6.3. Biomarkers: Recommendations

A. Ambulatory/Outpatient

Class I

1. In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty (217-223). *(Level of Evidence: A)*

2. Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (222, 224-229). *(Level of Evidence: A)*
NEW DEFINITION OF HEART FAILURE REQUIRES ELEVATED PLASMA NP
--for HFPEF and HFmrEF

Table 3.1  Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs(^a)</td>
<td>Symptoms ± Signs(^a)</td>
<td>Symptoms ± Signs(^a)</td>
</tr>
<tr>
<td>CRITERIA</td>
<td>2 LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td>3</td>
<td>1. Elevated levels of natriuretic peptides(^b); 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).</td>
<td>1. Elevated levels of natriuretic peptides(^b); 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

\(^b\)BNP >35 pg/ml and/or NT-proBNP > 125 pg/mL.
Upon presentation measurement of plasma NT-proBNP is recommended in **ALL** cases with acute dyspnea and suspected Acute Heart Failure.
ESC Guidelines for diagnosis and treatment of HF 2012
Troponin intra and extra-cellular locations

Can biomarker(s) improve current Risk Stratification and treatment decisions/efficacy?
Biomarkers in Heart Disease: the non-acute setting-

- There are TWO Cardinal Established Clinical CV Biomarkers
  - cardiac troponins
  - cardiac B type natriuretic peptides

Both established in acute cardiac disease - acute heart failure - acute heart attack (AMI)

Both increasingly recognized as sensitive predictors of CV Prognosis in pre-clinical and non-acute settings
Highly sensitive troponins knocking at the door of primary prevention

Evangelos Giannitsis* and Hugo A. Katus
Biomarkers applied in the general population?

- **NT-proBNP**: Amino-terminal pro-B type natriuretic peptide
- **TnT**: Measured with a new highly sensitive assay - lower detection limit (3 pg/mL)
- **GDF-15**: Growth differentiation factor-15
- **sFLT-1**: fms-tyrosine kinase-1 (VEGF receptor-1)
- **PLGF**: Placental growth factor
In 1982-1984: a random sample of 4807 individuals, aged 30, 40, 50 or 60 years were invited to participate in the Danish MONICA program.

In 1993-1994: 3785 former participants were re-invited to participate in the MONICA 10 program.

To evaluate the value of **NT-proBNP, hs cTnT, GDF-15,PLGF, and sFLT-1** for predicting first major cardiovascular events and death in the general population...
TNT and Outcome

First CV event

Overall mortality

Cumulative risk

Cumulative survival

hsTNT < 3 pg/mL

hsTNT ≥ 3 pg/mL

P < 0.001

Time (years)

hsTNT < 3 pg/mL

hsTNT ≥ 3 pg/mL

P < 0.001

Time (years)
### Adjusted HR for overall mortality

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDF-15 (&gt;528 pg/mL)</td>
<td>2.0 (1.4-2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hsTNT (&gt;3 pg/mL)</td>
<td>1.5 (1.2-2.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>PLGF (&gt;16 pg/mL)</td>
<td>1.3 (0.9-1.6)</td>
<td>0.062</td>
</tr>
<tr>
<td>FLT-1 (&gt;78 pg/mL)</td>
<td>1.6 (1.3-1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP (&gt;89 pg/mL)</td>
<td>1.5 (1.2-1.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>hsCRP (&gt;3.8 mg/L)</td>
<td>1.5 (1.2-1.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR adjusted for age, gender, diabetes, current smoking, systolic BP, hypertensive medication, serum total-cholesterol, serum HDL-cholesterol.
30 Markers
7915 from FINRISK 97
-538 incident CV events over 10y

2552 men
Belfast PRIME cohort
-260 events

Developed score cTnI, NT-proBNP, CRP
### Table 3. HRs of Future Cardiovascular Events According to Optimal Cut Points

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Data-Derived Optimal Cut Point*</th>
<th>Percentile</th>
<th>Belfast PRIME Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein</td>
<td>6.81 mg/L</td>
<td>93.1</td>
<td>91.0</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>187 pg/mL</td>
<td>94.5</td>
<td>97.2</td>
</tr>
<tr>
<td>Troponin I</td>
<td>0.008 ng/mL</td>
<td>91.9</td>
<td>97.6</td>
</tr>
<tr>
<td>Score: 0.38468×C-reactive protein$^{1/3}$ + 0.11005×NT-proBNP$^{1/3}$ + 1.27006×troponin I$^{1/3}$</td>
<td>1.35686</td>
<td>92.5</td>
<td>95.7</td>
</tr>
</tbody>
</table>

**Circulation** 2010;121:2388-97

Figure 2. Fully adjusted HRs of biomarkers for incident cardiovascular events. HRs are per 1-SD increment and are adjusted for age, area, body mass index, systolic blood pressure, diabetes mellitus, smoking, non-HDL cholesterol, HDL-cholesterol, and cardiovascular medication. Shown on the bottom is the HR associated with a continuous score derived from NT-proBNP, C-reactive protein, and troponin I. Apo indicates apolipoprotein; CI, confidence interval.
Epidemiology from community cohorts

Multi-Ethnic Study of Atherosclerosis “MESA”

Figure 2. Adjusted HRs for incident CHD (A) and CVD (B) by decile of NT-proBNP. HRs are adjusted for age, sex, race, current smoking (Y/N), family history of heart attack, diabetes, use of antihypertensive therapy, use of statin therapy, body mass index, SBP, ...

Lori B. Daniels, Paul Clopton, Christopher R. deFilippi, Otto A. Sanchez, Hossein Bahrami, Joao A.C. Lima, Russell P. Tracy, David Siscovick, Alain G. Bertoni, Philip Greenland, Mary Cushman, Alan S. Maisel, Michael H. Criqui

Serial measurement of N-terminal pro-B-type natriuretic peptide and cardiac troponin T for cardiovascular disease risk assessment in the Multi-Ethnic Study of Atherosclerosis (MESA)


http://dx.doi.org/10.1016/j.ahj.2015.09.010
Epidemiology from community cohorts

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American Heart Journal, 2015;170:1170–1183
http://dx.doi.org/10.1016/j.ahj.2015.09.010

Figure 3. Kaplan-Meier plots based on quintile of NT-proBNP, by ethnicity. The plots show risk of incident CHD and CVD among all participants (A,E), non-Hispanic whites (B,F), African Americans (C,G), and Hispanics (D,H).
Troponin T and N-Terminal Pro-B-Type Natriuretic Peptide: A Biomarker Approach to Predict Heart Failure Risk—The Atherosclerosis Risk in Communities Study

Vijay Nambi,1,2,3* Xiaoxi Liu,4 Lloyd E. Chambless,4 James A. de Lemos,5 Salim S. Virani,1,2 Sunil Agarwal,6 Eric Boerwinkle,7 Ron C. Hoogeveen,2 David Aguilar,2 Brad C. Astor,8 Pothur R. Srinivas,9 Anita Deswal,1,2 Thomas H. Mosley,10 Josef Coresh,6 Aaron R. Folsom,11 Gerardo Heiss,4 and Christie M. Ballantyne2,3

METHODS: Using sex-specific models, we added cTnT and NT-proBNP to age and race (“laboratory report” model) and to the ARIC HF model (includes age, race, systolic blood pressure, antihypertensive medication use, current/former smoking, diabetes, body mass index, prevalent coronary heart disease, and heart rate) in 9868 participants without prevalent HF; area under the receiver operating characteristic curve (AUC), integrated discrimination improvement, net reclassification improvement (NRI), and model fit were described.
Models:

Model 1: age, race, systolic blood pressure (SBP), antihypertensive medication use, current smoking, former smoking, diabetes, body mass index (BMI), prevalent coronary heart disease (CHD), heart rate (ARIC HF model)

Model 2: Model 1 + cTnT + NT-proBNP (ARIC HF + biomarker model)

Model 3: age, race, cTnT + NT-proBNP (lab report model)

Note: Troponin modeled as 6 categories and log(NT-proBNP) were used.

**Fig. 2. Ten-year risk of HF by decile of estimated risk.**

In this figure, we describe, in men and women, the number of individuals in each decile of risk who will have incident HF in 10 years.

**RESULTS:** Over a mean follow-up of 10.4 years, 970 participants developed incident HF. Adding cTnT and NT-proBNP to the ARIC HF model significantly improved all statistical parameters (AUCs increased by 0.040 and 0.057; the continuous NRIs were 50.7% and 54.7% in women and men, respectively). Interestingly,
**Troponin T and N-Terminal Pro-B-Type Natriuretic Peptide: A Biomarker Approach to Predict Heart Failure Risk—The Atherosclerosis Risk in Communities Study**

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Goodness of model fit: Grønnesby–Borgan test statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>Men</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.653 (0.628–0.676)</td>
<td>0.658 (0.634–0.682)</td>
</tr>
<tr>
<td>Model 2 (ARIC HF model)</td>
<td>0.779 (0.763–0.800)</td>
<td>0.776 (0.760–0.797)</td>
</tr>
<tr>
<td>Model 3 (lab model)</td>
<td>0.789 (0.767–0.812)</td>
<td>0.767 (0.745–0.789)</td>
</tr>
<tr>
<td>Model 4 (ARIC HF + biomarkers model)</td>
<td>0.836 (0.821–0.857)</td>
<td>0.817 (0.803–0.837)</td>
</tr>
<tr>
<td>Model 2 + cTnT</td>
<td>0.811 (0.797–0.833)</td>
<td>0.804 (0.790–0.825)</td>
</tr>
<tr>
<td>Model 2 + NT-proBNP</td>
<td>0.822 (0.805–0.843)</td>
<td>0.804 (0.789–0.826)</td>
</tr>
</tbody>
</table>

*Model 1, age + race; model 2, ARIC HF model; model 3, model 1 + cTnT + NT-proBNP (lab model); model 4, model 2 + cTnT + NT-proBNP (ARIC HF + biomarkers model). 95% CI was generated using 1000 bootstraps. ARIC HF model includes age, race, systolic blood pressure, antihypertensive medication use, current/former smoking, diabetes, body mass index, prevalent CHD, and heart rate. Biomarkers refer to cTnT and NT-proBNP. Lab model includes age, race, cTnT, and NT-proBNP.*
Broadening and improving cardiovascular risk assessment with natriuretic peptides measurement: individual-participant meta-analysis of 40 prospective cohorts. 

The Natriuretic Peptides Studies Collaboration

Data from 40 prospective cohorts involving 95,617 participants without a history of CVD at baseline. Follow up median 7.8 years.

Risk ratios = adjusted for age, smoking status, history of diabetes, systolic blood pressure, total cholesterol and HDL-C and, where appropriate, stratified by sex. Total of:
- 4,716 CHD outcomes (from 34 cohorts)
- 3,760 stroke outcomes (from 29 cohorts)
- 2,008 heart failure outcomes (from 14 cohorts).

**Interpretation:** In people without baseline CVD, adding NT-proBNP assessment to conventional risk factors could improve accuracy of CHD and stroke risk prediction as well as broaden CVD prediction to include first-onset heart failure.
IS THERE ANY TRIAL EVIDENCE SUPPORTING EFFICACY OF MARKER-GUIDED RISK STRATIFICATION TO TRIGGER TREATMENT?
Figure 1 Kaplan–Meier curves of all-cause mortality or unplanned cardiovascular hospitalization in 631 diabetic patients according to plasma-levels of NT-proBNP at baseline. Solid line: patients with NT-proBNP levels below cut-off (<125 pg/mL). Dashed line: patients with NT-proBNP levels above cut-off (>125 pg/mL). Log-rank test for overall difference, $P < 0.0001$. 
Inclusion Criteria
Type 2 DM ≥ 6/12
Age ≥ 18 years
NT-proBNP > 125pg/ml

Exclusion Criteria
-Hx of Cardiac Disease
-ECG changes incl Afib, ST-T wave abnormalities, BBB
-Abnormal Echo (with exception of diastolic dysfunction) i.e low EF, wall motion abnormalities, significant valve dysfunction
- Expectancy < 1 year
- Chronic Infections
- Cortisone Rx
- Renal replacement Rx
- Childbearing age sans reliable contraception

INTERVENTION
Maximized RAAS / Beta blockade
Versus
Usual Care
Flow Diagram

Enrollment, randomization, and follow-up of study participants.
Table 2  Baseline Characteristics and Follow-Up Values

<table>
<thead>
<tr>
<th></th>
<th>Control Baseline (n = 150)</th>
<th>Intensified Baseline (n = 150)</th>
<th>p Value</th>
<th>Control 12 Months (n = 131)</th>
<th>Intensified 12 Months (n = 137)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure systolic, mm Hg</td>
<td>151 ± 22</td>
<td>151 ± 23</td>
<td>0.10</td>
<td>144 ± 22*</td>
<td>145 ± 22*</td>
<td>0.83</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>72 ± 11</td>
<td>72 ± 12</td>
<td>0.78</td>
<td>72 ± 12</td>
<td>68 ± 11*</td>
<td>0.004</td>
</tr>
<tr>
<td>RAS antagonist, %</td>
<td>79</td>
<td>77</td>
<td>0.78</td>
<td>78</td>
<td>95*</td>
<td>0.0001</td>
</tr>
<tr>
<td>RAS % target dose</td>
<td>55 ± 40</td>
<td>57 ± 42</td>
<td>0.59</td>
<td>74 ± 31*</td>
<td>92 ± 30*</td>
<td>0.0001</td>
</tr>
<tr>
<td>Beta-blocker, %</td>
<td>45</td>
<td>54</td>
<td>0.13</td>
<td>44</td>
<td>85*</td>
<td>0.0001</td>
</tr>
<tr>
<td>Beta-blocker % target dose</td>
<td>24 ± 32</td>
<td>32 ± 35</td>
<td>0.05</td>
<td>54 ± 29*</td>
<td>80 ± 31*</td>
<td>0.0001</td>
</tr>
<tr>
<td>Statins</td>
<td>71 (47.3%)</td>
<td>72 (48.0%)</td>
<td>0.10</td>
<td>61 (40.7%)</td>
<td>70 (46.7%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Aspirin</td>
<td>62 (41.3%)</td>
<td>63 (42.0%)</td>
<td>1.0</td>
<td>51 (34.0%)</td>
<td>63 (42.0%)</td>
<td>0.098</td>
</tr>
<tr>
<td>Oral antidiabetic drugs</td>
<td>68 (45.3%)</td>
<td>71 (47.3%)</td>
<td>0.62</td>
<td>61 (40.7%)</td>
<td>67 (44.7%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Insulin</td>
<td>45 (30.0%)</td>
<td>42 (28.0%)</td>
<td>0.73</td>
<td>44 (29.3%)</td>
<td>35 (23.3%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>154 ± 76</td>
<td>152 ± 70</td>
<td>0.83</td>
<td>146 ± 85</td>
<td>151 ± 85</td>
<td>0.63</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>96 ± 33</td>
<td>94 ± 29</td>
<td>0.34</td>
<td>94 ± 32</td>
<td>89 ± 29*</td>
<td>0.21</td>
</tr>
<tr>
<td>eGFR, ml/min</td>
<td>81.5 ± 18.2</td>
<td>82.9 ± 18.2</td>
<td>0.51</td>
<td>82.2 ± 18.7</td>
<td>77 ± 17.6*</td>
<td>0.14</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.9 ± 1</td>
<td>7.1 ± 1</td>
<td>0.27</td>
<td>7.1 ± 1.2*</td>
<td>7.1 ± 1</td>
<td>0.78</td>
</tr>
<tr>
<td>NT-proBNP, pg/ml</td>
<td>266 (181-402)</td>
<td>235 (169-343)</td>
<td>0.18</td>
<td>264 (167-394)</td>
<td>248 (169-433)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Values are mean ± SD, %, n (%), or median (interquartile range). *p < 0.05 baseline versus 12 months within a group. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.11429. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

eGFR = estimated glomerular filtration rate; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RAS = renin-angiotensin system.
Figure 2
Kaplan-Meier Curves of the Primary Endpoint
Hospitalization or Death Due to Cardiac Disease
According to Treatment Strategy

Red line = intensified group. Blue line = control group. Log-rank test for overall difference, p = 0.035.

Table 3
Reasons for Hospitalizations

<table>
<thead>
<tr>
<th>Hospitalization Due to</th>
<th>All</th>
<th>Control</th>
<th>Intensified</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any reason</td>
<td>135 (45%)</td>
<td>77 (51%)</td>
<td>58 (39%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>25 (8%)</td>
<td>18 (12%)</td>
<td>7 (5%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac event</td>
<td>19 (6%)</td>
<td>14 (9%)</td>
<td>5 (3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8 (3%)</td>
<td>7 (5%)</td>
<td>1 (1%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Original Investigation

Natriuretic Peptide-Based Screening and Collaborative Care for Heart Failure
The STOP-HF Randomized Trial

Mark Ledwidge, PhD; Joseph Gallagher, MB; Carmel Conlon, PhD; Elaine Tallon, PGDip; Eoin O'Connell, MLitt; Ian Dawkins, DPhil; Chris Watson, PhD; Rory O’Hanlon, MD; Margaret Bermingham, BSc(Pharm); Anil Patle, MBA; Mallikarjuna R. Badabagni, RDCS; Gillian Murtagh, MD; Victor Voon, MB; Leslie Tilson, PhD; Michael Barry, MD; Laura McDonald; Brian Maurer, MD; Kenneth McDonald, MD

Inclusion Criteria

- Over 40 years
- 1 or more of:
  - Hypertension (Rx ≥ 1/12)
  - Hypercholesterolemia (TC > 5.0 mmol/L and/ or LDL > 3.0 mmol/L or on anti-lipid Rx)
  - Obesity (BMI > 30)
  - Vascular Disease incl coronary artery disease, Cerebrovasc disease and PVD
  - Diabetes
  - Arrhythmia requiring Rx
  - Mod to severe valve disease

Exclusion Criteria

- Refusal to consent
- Established LV systolic dysfunction
- Evidence or Hx of symptomatic HF
- Survival < study period

STOP-HF
The Intervention
Consecutive consenting patients fulfilling Incl and not Excl criteria recruited by Study Nurse and randomized 1:1 to :

CONTROL
Per Primary Care :
• Advice on lifestyle modifications
• Risk Factor intervention as determined
• ≥ 1 Annual review
• No knowledge of BNP result - repeated annually by Nurse and referred if BNP moved to > 50pg/ml

INTERVENTION
• BNP results to Primary Care
• BNP < 50pg/ml managed as control (albeit with disclosure of BNP values to patients and their primary care physicians)
• BNP>50pg/ml = referred to Cardiovascular Service
• Doppler Echo and review by Cardiologist -> decided on any further Dx or Rx
• Multi-dimensional Rx  = optimal risk factor management
  - coaching by specialist nurse, lifestyle, adherence to meds
  - collaborative care, ≥ 1 annual specialist review, incl repeat echo, repeat BNP and other Dx’s as appropriate … all conveyed to Primary Care giver.

FINAL:-- At trial termination ALL CONTROL and INTERVENTION underwent blinded Echo and Clinical Assessment.

STOP-HF
Figure 1. Participant Flow

3123 Patients assessed for eligibility

1749 Excluded
   1203 Did not meet inclusion criteria
   546 Declined to participate

1374 Randomized

697 Randomized to receive BNP screening and protocol referral for BNP ≥50 pg/mL to specialist cardiovascular center (collaborative care)
   697 Received BNP screening as randomized
   263 With BNP ≥50 pg/mL received Doppler echocardiography and collaborative care follow-up

535 Completed follow-up
   70 Lost to follow-up (not contactable)
   92 Withdrew from study
   61 Not interested in further participation
   17 Unable to attend study visits
   9 Moved out of area or changed physician
   5 Other reasons

697 Included in analysis

677 Randomized to receive usual primary care physician management
   677 Received usual care as randomized

476 Completed follow-up
   69 Lost to follow-up (not contactable)
   132 Withdrew from study
   83 Not interested in further participation
   34 Unable to attend study visits
   8 Moved out of area or changed physician
   7 Other reasons

677 Included in analysis

BNP indicates brain-type natriuretic peptide.

Table 2. End-Point Prevalence Analysis

<table>
<thead>
<tr>
<th>End-Point Events</th>
<th>No. (%) of Participants</th>
<th>Unadjusted Multiple Imputation, OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted Multiple Imputation, OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>n=677</td>
<td>n=697</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure or LVD</td>
<td>59 (8.7)</td>
<td>37 (5.3)</td>
<td>0.55 (0.37-0.82)</td>
<td>.003</td>
<td>0.57 (0.38-0.86)</td>
</tr>
<tr>
<td>Heart failure or LVSD</td>
<td>33 (4.9)</td>
<td>23 (3.3)</td>
<td>0.63 (0.38-1.04)</td>
<td>.07</td>
<td>0.65 (0.38-1.09)</td>
</tr>
<tr>
<td>Asymptomatic LVSD</td>
<td>19 (2.8)</td>
<td>16 (2.3)</td>
<td>0.73 (0.38-1.40)</td>
<td>.34</td>
<td>0.70 (0.37-1.31)</td>
</tr>
<tr>
<td>Asymptomatic LVDD</td>
<td>26 (3.8)</td>
<td>14 (2.0)</td>
<td>0.51 (0.28-0.92)</td>
<td>.03</td>
<td>0.58 (0.32-1.06)</td>
</tr>
<tr>
<td>Asymptomatic LVD</td>
<td>45 (6.6)</td>
<td>30 (4.3)</td>
<td>0.57 (0.37-0.88)</td>
<td>.01</td>
<td>0.60 (0.39-0.93)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>29 (4.3)</td>
<td>21 (3.0)</td>
<td>0.72 (0.43-1.23)</td>
<td>.23</td>
<td>0.77 (0.45-1.32)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>14 (2.1)</td>
<td>7 (1.0)</td>
<td>0.48 (0.20-1.20)</td>
<td>.12</td>
<td>0.52 (0.21-1.32)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 (1.6)</td>
<td>8 (1.1)</td>
<td>0.71 (0.30-1.72)</td>
<td>.45</td>
<td>0.71 (0.29-1.74)</td>
</tr>
<tr>
<td>Pulmonary embolism/deep vein thrombosis</td>
<td>10 (1.5)</td>
<td>4 (0.6)</td>
<td>0.51 (0.18-1.44)</td>
<td>.21</td>
<td>0.47 (0.16-1.40)</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>28 (4.1)</td>
<td>13 (1.9)</td>
<td>0.48 (0.26-0.91)</td>
<td>.02</td>
<td>0.51 (0.27-0.96)</td>
</tr>
<tr>
<td>Major adverse cardiovascular eventsa</td>
<td>71 (10.5)</td>
<td>51 (7.3)</td>
<td>0.69 (0.49-0.98)</td>
<td>.04</td>
<td>0.72 (0.50-1.03)</td>
</tr>
<tr>
<td>Participants with BNP ≥50 pg/mL</td>
<td>n=235</td>
<td>n=263</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure or LVD</td>
<td>44 (18.7)</td>
<td>25 (9.5)</td>
<td>0.44 (0.26-0.73)</td>
<td>.002</td>
<td>0.46 (0.27-0.79)</td>
</tr>
<tr>
<td>Heart failure or LVSD</td>
<td>29 (12.3)</td>
<td>17 (6.5)</td>
<td>0.46 (0.24-0.90)</td>
<td>.03</td>
<td>0.48 (0.24-0.97)</td>
</tr>
<tr>
<td>Asymptomatic LVSD</td>
<td>17 (7.2)</td>
<td>12 (4.6)</td>
<td>0.52 (0.24-1.14)</td>
<td>.11</td>
<td>0.51 (0.24-1.06)</td>
</tr>
<tr>
<td>Asymptomatic LVDD</td>
<td>15 (6.4)</td>
<td>8 (3.0)</td>
<td>0.48 (0.21-1.07)</td>
<td>.08</td>
<td>0.58 (0.26-1.30)</td>
</tr>
<tr>
<td>Asymptomatic LVD</td>
<td>32 (13.6)</td>
<td>20 (7.6)</td>
<td>0.47 (0.27-0.83)</td>
<td>.01</td>
<td>0.50 (0.28-0.90)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>23 (9.8)</td>
<td>18 (6.8)</td>
<td>0.69 (0.36-1.31)</td>
<td>.26</td>
<td>0.71 (0.37-1.36)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12 (5.1)</td>
<td>5 (1.9)</td>
<td>0.43 (0.15-1.19)</td>
<td>.11</td>
<td>0.47 (0.16-1.33)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6 (2.6)</td>
<td>2 (0.8)</td>
<td>0.31 (0.06-1.65)</td>
<td>.17</td>
<td>0.29 (0.05-1.53)</td>
</tr>
<tr>
<td>Pulmonary embolism/deep vein thrombosis</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
<td>0.30 (0.06-1.50)</td>
<td>.14</td>
<td>0.30 (0.05-1.62)</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>14 (6)</td>
<td>9 (3.4)</td>
<td>0.57 (0.25-1.31)</td>
<td>.19</td>
<td>0.67 (0.28-1.57)</td>
</tr>
<tr>
<td>Major adverse cardiovascular eventsa</td>
<td>45 (19.1)</td>
<td>35 (13.3)</td>
<td>0.65 (0.40-1.05)</td>
<td>.08</td>
<td>0.68 (0.41-1.11)</td>
</tr>
</tbody>
</table>

Abbreviations: BNP, brain-type natriuretic peptide; LVD, left ventricular dysfunction; LVDD, left ventricular diastolic dysfunction; LVSD, left ventricular systolic dysfunction; OR, odds ratio.
a Major adverse cardiovascular events included arrhythmia, heart failure, myocardial infarction, pulmonary embolism/deep vein thrombosis, stroke, and transient ischemic attack.
Figure 2. Kaplan-Meier Analysis of Major Adverse Cardiovascular Events in the Full Study Sample and in Participants With BNP ≥ 50 pg/mL

No. at risk
Intervention: 697, 605, 582, 533, 441, 305, 141, 41
Control: 677, 587, 558, 501, 418, 296, 118, 27

In the full sample, 51 (7.3%) of 697 patients were admitted for major adverse cardiovascular events in the intervention group and 71 (10.5%) of 677 were admitted in the control group. In participants with BNP ≥ 50 pg/mL, 35 (13.3%) of 263 were admitted for major adverse cardiovascular events in the intervention group and 45 (19.1%) of 235 were admitted in the control group.

BNP indicates brain-type natriuretic peptide.
### Table 3. Event Rate Analysis

<table>
<thead>
<tr>
<th>Events</th>
<th>No. of Events</th>
<th>No. of Person-Years</th>
<th>Events per 1000 Person-Years</th>
<th>Unadjusted Multiple Imputation, IRR (95% CI)</th>
<th>P Value</th>
<th>Adjusted Multiple Imputation, IRR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>45</td>
<td>29</td>
<td>2898.26 2917.16</td>
<td>15.5</td>
<td>.9</td>
<td>0.69 (0.43-1.12)</td>
<td>.13</td>
</tr>
<tr>
<td>Heart failure</td>
<td>18</td>
<td>8</td>
<td>2898.26 2917.16</td>
<td>6.2</td>
<td>.09</td>
<td>0.47 (0.20-1.09)</td>
<td>.19</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11</td>
<td>8</td>
<td>2898.26 2917.16</td>
<td>3.8</td>
<td>.31</td>
<td>0.73 (0.31-1.75)</td>
<td>.13</td>
</tr>
<tr>
<td>Pulmonary embolism/deep vein thrombosis</td>
<td>11</td>
<td>4</td>
<td>2898.26 2917.16</td>
<td>3.8</td>
<td>.17</td>
<td>0.50 (0.18-1.39)</td>
<td>.15</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>32</td>
<td>16</td>
<td>2898.26 2917.16</td>
<td>11</td>
<td>.05</td>
<td>0.53 (0.29-0.96)</td>
<td>.09</td>
</tr>
<tr>
<td>Major adverse cardiovascular events</td>
<td>117</td>
<td>65</td>
<td>2898.26 2917.16</td>
<td>40.4</td>
<td>.002</td>
<td>0.60 (0.45-0.81)</td>
<td>.006</td>
</tr>
<tr>
<td>Participants with BNP ≥50 pg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>38</td>
<td>25</td>
<td>1051.17 1150.29</td>
<td>36.2</td>
<td>.09</td>
<td>0.62 (0.37-1.04)</td>
<td>.08</td>
</tr>
<tr>
<td>Heart failure</td>
<td>16</td>
<td>5</td>
<td>1051.17 1150.29</td>
<td>15.2</td>
<td>.06</td>
<td>0.35 (0.13-0.98)</td>
<td>.07</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6</td>
<td>2</td>
<td>1051.17 1150.29</td>
<td>5.7</td>
<td>.16</td>
<td>0.32 (0.06-1.68)</td>
<td>.13</td>
</tr>
<tr>
<td>Pulmonary embolism/deep vein thrombosis</td>
<td>5</td>
<td>2</td>
<td>1051.17 1150.29</td>
<td>4.8</td>
<td>.14</td>
<td>0.31 (0.06-1.55)</td>
<td>.18</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>17</td>
<td>12</td>
<td>1051.17 1150.29</td>
<td>16.2</td>
<td>.2</td>
<td>0.64 (0.31-1.34)</td>
<td>.32</td>
</tr>
<tr>
<td>Major adverse cardiovascular events</td>
<td>82</td>
<td>46</td>
<td>1051.17 1150.29</td>
<td>78</td>
<td>.002</td>
<td>0.56 (0.39-0.81)</td>
<td>.004</td>
</tr>
</tbody>
</table>

Abbreviations: BNP, brain-type natriuretic peptide; IRR, incidence rate ratio. * Major adverse cardiovascular events included arrhythmia, heart failure, myocardial infarction, pulmonary embolism/deep vein thrombosis, stroke, and transient ischemic attack.
### eTable 3. Prescribed Drugs at Baseline and Follow-up

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Baseline Control</th>
<th>Baseline Intervention</th>
<th>Follow up Control</th>
<th>Follow up Intervention</th>
<th>Chi-square p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td>677</td>
<td>697</td>
<td>677</td>
<td>697</td>
<td></td>
</tr>
<tr>
<td>Alpha Blockers</td>
<td>15 (2.2%)</td>
<td>24 (3.4%)</td>
<td>24 (3.5%)</td>
<td>28 (4.0%)</td>
<td>.23</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>169 (25.0%)</td>
<td>187 (26.8%)</td>
<td>198 (29.2%)</td>
<td>219 (31.4%)</td>
<td>.47</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>102 (15.1%)</td>
<td>113 (16.2%)</td>
<td>147 (21.7%)</td>
<td>166 (23.8%)</td>
<td>.61</td>
</tr>
<tr>
<td>Statins</td>
<td>355 (52.4%)</td>
<td>368 (52.8%)</td>
<td>405 (59.8%)</td>
<td>421 (60.4%)</td>
<td>.94</td>
</tr>
<tr>
<td>Anti-Platelet</td>
<td>267 (39.4%)</td>
<td>296 (42.5%)</td>
<td>290 (42.8%)</td>
<td>317 (45.5%)</td>
<td>.28</td>
</tr>
<tr>
<td>Diuretics</td>
<td>141 (20.8%)</td>
<td>128 (18.4%)</td>
<td>203 (30%)</td>
<td>207 (29.7%)</td>
<td>.28</td>
</tr>
<tr>
<td>AA, N (%)</td>
<td>3 (0.4%)</td>
<td>3 (0.4%)</td>
<td>4 (0.6%)</td>
<td>6 (0.9%)</td>
<td>-</td>
</tr>
<tr>
<td>ARB, N (%)</td>
<td>126 (18.6%)</td>
<td>155 (22.2%)</td>
<td>167 (24.7%)</td>
<td>226 (32.4%)</td>
<td>.11</td>
</tr>
<tr>
<td>ACEI, N (%)</td>
<td>167 (24.7%)</td>
<td>157 (22.5%)</td>
<td>180 (26.6%)</td>
<td>177 (25.4%)</td>
<td>.38</td>
</tr>
<tr>
<td>Any AA, ARB or ACEI, N (%)</td>
<td>282 (41.7%)</td>
<td>299 (42.9%)</td>
<td>336 (49.6%)</td>
<td>394 (55.5%)</td>
<td>.68</td>
</tr>
<tr>
<td><strong>BNP ≥50 pg/mL Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha Blockers</td>
<td>6 (2.6%)</td>
<td>14 (5.3%)</td>
<td>9 (3.8%)</td>
<td>15 (5.7%)</td>
<td>.18</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>87 (37.0%)</td>
<td>117 (44.5%)</td>
<td>115 (48.9%)</td>
<td>133 (50.6%)</td>
<td>.11</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>47 (20.0%)</td>
<td>54 (20.5%)</td>
<td>64 (27.2%)</td>
<td>81 (30.3%)</td>
<td>.97</td>
</tr>
<tr>
<td>Statins</td>
<td>137 (58.3%)</td>
<td>149 (56.7%)</td>
<td>155 (66.0%)</td>
<td>179 (66.1%)</td>
<td>.78</td>
</tr>
<tr>
<td>Anti-Platelet</td>
<td>117 (49.8%)</td>
<td>143 (54.4%)</td>
<td>123 (52.3%)</td>
<td>151 (57.4%)</td>
<td>.35</td>
</tr>
<tr>
<td>Diuretics</td>
<td>67 (28.5%)</td>
<td>69 (26.2%)</td>
<td>98 (41.7%)</td>
<td>106 (40.3%)</td>
<td>.64</td>
</tr>
<tr>
<td>AA, N (%)</td>
<td>2 (0.9%)</td>
<td>2 (0.8%)</td>
<td>2 (0.9%)</td>
<td>4 (1.5%)</td>
<td>-</td>
</tr>
<tr>
<td>ARB, N (%)</td>
<td>50 (21.3%)</td>
<td>77 (29.3%)</td>
<td>65 (27.7%)</td>
<td>116 (44.1%)</td>
<td>.05</td>
</tr>
<tr>
<td>ACEI, N (%)</td>
<td>66 (28.1%)</td>
<td>79 (30.0%)</td>
<td>76 (32.3%)</td>
<td>86 (32.7%)</td>
<td>.70</td>
</tr>
<tr>
<td>Any AA, ARB or ACEI, N (%)</td>
<td>112 (47.7%)</td>
<td>147 (55.9%)</td>
<td>134 (57.0%)</td>
<td>195 (74.1%)</td>
<td>.08</td>
</tr>
</tbody>
</table>

AA – Aldosterone Antagonists, ARB – Angiotensin Receptor Blockers, ACEI – Angiotensin-Converting-Enzyme Inhibitors

Cost-effectiveness of natriuretic peptide-based screening and collaborative care: a report from the STOP-HF (St Vincent’s Screening TO Prevent Heart Failure) study

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1St Vincent’s University Hospital, Chronic Cardiovascular Disease Management Unit, Dublin, Ireland; 2School of Medicine and Medical Science, University College Dublin, Dublin, Ireland; 3St James Hospital, National Centre for Pharmaco-economics, Dublin, Ireland; and 4School of Pharmacy, University College, Cork, Ireland

Received 14 November 2014; revised 27 March 2015; accepted 31 March 2015

Aims
Prevention of cardiovascular disease and heart failure (HF) in a cost-effective manner is a public health goal. This work aims to assess the cost-effectiveness of the St Vincent’s Screening TO Prevent Heart Failure (STOP-HF) intervention.

Methods
This is a sub-study of 1054 participants with cardiovascular risk factors [median age 65.8 years, interquartile range (IQR) 57.8-72.4, with 4.3 years, IQR 3.4-5.2, follow-up]. Annual natriuretic peptide-based screening was performed, with collaborative cardiovascular care between specialist physicians and general practitioners provided to patients with BNP levels >50 pg/mL. Analysis of cost per case prevented and cost-effectiveness per quality-adjusted life year (QALY) gained was performed. The primary clinical endpoint of LV dysfunction (LVD) with or without HF was reduced in intervention patients [odds ratio (OR) 0.60; 95% confidence interval (CI) 0.38–0.94; P = 0.026]. There were 157 deaths and/or emergency hospitalizations for major adverse cardiac events (MACE) in the control group vs. 102 in the intervention group (OR 0.68; 95% CI 0.49–0.93; P = 0.01). The cost per case of LVD/HF prevented was €9683 (sensitivity range −€843 to €20 210), whereas the cost per MACE prevented was €3471 (sensitivity range −€302 to €7245). Cardiovascular hospitalization savings offset increased outpatient and primary care costs. The cost per QALY gain was €1104 and the intervention has an 88% probability of being cost-effective at a willingness to pay threshold of €30 000.
An NT-proBNP-guided preventative intervention with an intervention effect size (4-year hazard ratio for intervention in biomarker positive cohort) of ≤ 0.7 would reduce the global burden of HF by ≥ 20% and MACE by ≥ 15%. Per this simulation, the NNS to prevent one HF event or MACE in four years would be ≤ 100 with a NNT to prevent one HF event of ≤ 20 and one MACE of ≤ 10.
Figure 3

- NT-proBNP
- NT-proBNP+hs-cTnI

**HF Prevention**

- NNT
  - 32% at 0.6
  - 26% at 0.7
  - 19% at 0.8
  - 13% at 0.9
  - 6% at 1.0

**MACE Prevention**

- NNT
  - 30% at 0.6
  - 22% at 0.7
  - 16% at 0.8
  - 11% at 0.9
  - 5% at 1.0

**HF Prevention**

- NNS
  - 400 at 0.6
  - 300 at 0.7
  - 200 at 0.8
  - 100 at 0.9
  - 50 at 1.0

**MACE Prevention**

- NNS
  - 250 at 0.6
  - 150 at 0.7
  - 100 at 0.8
  - 50 at 0.9
  - 25 at 1.0
NZ Proposal: Early N Terminal pro BNP Triggered Treatment to Reduce Adverse Cardiovascular Events (“ENTTRANCE”)

Foundation Work:
1. Consolidate NZ national team: epidemiology, cardiology, general medicine, primary care, clinical trialists.
2. Interrogate “PREDICT” Primary Care decision support/data base to update contemporary risk -> event relationships.
3. Assay NT-proBNP and hs TnT/TnI in over 8,000 community dwelling NZ’ers with documented follow-up
4. Assess additional risk stratification offered by adding NT-proBNP /hsTn to conventional profiling.
5. Define population in equipoise re intervention.
6. Design adequately-powered trial of intensified intervention following modified STOP-HF design.
7. Engagement with stakeholders.
8. Engagement with Maori.

Randomized Controlled Trials
1. Primary prevention informed by 1-8 above.
2. Secondary prevention (1 year post ACS) informed by CDCS data.

THANK YOU FOR YOUR ATTENTION